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Modern Concepts of Cardiovascular Disease

Published monthly by the AMERICAN HEART ASSOCIATION
44 EAST 23RD STREET, NEW YORK 10, N. Y.

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Vol. XXV **JULY 1956** **No. 7**

THE CARDIOVASCULAR MANIFESTATIONS OF FUNCTIONING CARCINOID TUMORS*

Historical

For many years, occasional case reports have appeared in the medical literature of peculiar cutaneous vasomotor phenomena, valvular and endocardial lesions of the right side of the heart, and the occurrence of terminal heart failure in patients with metastatic abdominal tumors. Patients who had these lesions were first thought to have unrelated diseases of the intestine, the skin, and the heart[1]. In time, the abdominal lesions became well identified histologically as *metastatic intestinal carcinoid tumors.*

During the past three years, the clinical concept of "functioning" carcinoid tumors developed following the isolation of a pharmacodynamic substance, 5-hydroxytryptamine, from such metastatic tumors[2]. The release of this substance from the tumor into the circulation was considered responsible for the production of the associated symptoms and pathological lesions—thus relating the heart disease and skin manifestations to the tumor[3]. This concept was fortified by the recognition that 5-hydroxytryptamine was identical to enteramine, a substance produced by the chromaffin cells of the intestinal tract[4], and serotonin, a substance previously found in the blood[5]. Furthermore, various investigators[6,7] found that serotonin had potent pharmacologic effects on the smooth muscle of the intestine, bronchi, and blood vessels. In 1954, studies in the laboratories of the National Heart Institute showed that serotonin was derived from the essential amino acid, tryptophan, and that an end product of this metabolic process was 5-hydroxyindoleacetic acid (5-HIAA) which is excreted in the urine[8].

Patients having the clinical features of a functioning carcinoid tumor were found to have an abnormal amount of serotonin in their circulating blood (hyperserotoninemia). They also excreted a large amount of 5-HIAA in their urine, and demonstrated a concomitant disorder of tryptophan metabolism[9].

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Present Concept of a Functioning Carcinoid Tumor

The present concept of a functioning carcinoid tumor is, therefore, based on the assumptions that: (1) the chromaffin cells of the normal intestinal tract "en masse" constitute a normal functioning secretory gland, producing a substance chemically identified as *5-hydroxytryptamine* or better known as *serotonin;* (2) the serotonin produced is liberated into the blood and/or lymph and has certain physiological activities; and (3) carcinoid tumors have their origin in these secretory cells and under certain conditions produce excessive amounts of serotonin. When released into the body and not promptly inactivated, this substance directly or indirectly, through altered tryptophan metabolism, causes exaggerated physiological activity and pathological changes in distant organs and tissues.

The clinical features occurring in patients with such functioning tumors are quite similar and distinctive, being referred to in current medical literature as the "Thorson-Biörck Syndrome," or the "malignant carcinoid syndrome". The clinical and biochemical features of a functioning carcinoid tumor permit easier diagnosis than other functioning tumors, such as the pheochromocytoma of the adrenal gland, or the islet cell tumor of the pancreas. The frequency with which case reports have appeared in the literature since this entity has been publicized suggests that it is not uncommon. The terms "carcinoid heart disease" and "serotonin heart disease" have already appeared in the literature. This etiology should be considered in the differential diagnosis of patients with cutaneous vasomotor phenomena of flushing and cyanosis, valvular heart disease involving the right side of the heart, hepatomegaly or low grade malignancies of the intestinal tract.

Pathology

In a recent review of 38 cases of functioning carcinoids as reported in the literature[10], it was noted that the primary tumor, when identified, was located in the small intestine, chiefly in the lower third of the ileum. Pathologic and clinical evidence of a functioning tumor occurred only

in patients where there was metastasis to the liver or other areas of the abdominal and pelvic cavities. Metastasis to the liver is important since it was present in 26 of 27 autopsied patients and absent in only two of all living and deceased patients who had features of a functioning tumor to date. Ovarian metastasis was common in female patients. Histological and histochemical studies of the tumors have failed to identify any specific biologic characteristic of the functioning tumor to differentiate it from the silent carcinoid tumor localized to the submucosal regions of the intestinal tract, but further observations are needed.

The recognized cardiovascular pathology as it relates to, or is associated with functioning carcinoids consist of: (1) fibrotic changes in the endocardium of the heart, chiefly of the right side of the heart but not limited thereto, and involving the mural portion as well as the valves and tendinous cords with resulting valvular deformities, and (2) dilatation of the capillaries, venules, and small veins of the skin with the development of miliary and gross telangiectasia and mild thickening of the skin. The most important result of the lesions in the heart is the appearance of deformities of the pulmonary and tricuspid valves. The ensuing hemodynamic changes cause right-sided heart failure similar to that seen with pulmonary and/or tricuspid stenosis, or tricuspid insufficiency from other causes, either congenital or acquired.

Pulmonary valve stenosis is the most common result of this lesion and is often severe. In the tricuspid valve, fibrosis and thickening occurs, but since the process commonly involves the tendinous cords with fibrosis and shortening, valvular insufficiency is more frequent than stenosis. However, severe stenosis has been seen in three patients. Generally, there is some deformity of both valves, the usual combination being pulmonary stenosis and tricuspid insufficiency. Valvular lesions were found in 21 out of 27 patients on whom an autopsy had been performed. Scattered or diffuse endocardial fibrosis and thickening of the wall of the right atrium and ventricle was always present to some degree in the patients with valve lesions and at times this was pronounced. Only scanty mention has been made of sclerotic changes in the vena cava or the main pulmonary artery or its branches. No distinctive pathological changes have been found in the lungs or the pulmonary vasculature. Right ventricular hypertrophy of a significant degree developed where the pulmonary valve stenosis was pronounced, and usually the right atrium was abnormally dilated as a result of tricuspid valve deformity or relative valvular insufficiency. Congestive phenomena similar to those occurring in right-sided heart failure from other causes were frequently found at autopsy. These phenomena include: pleural effusion, hepatic congestion (as well as hepatic tumor metastasis), ascites and edema of the lower extremities. Congestion below the level of the diaphragm may not be related in all instances to a failing heart. For instance, obstructive lesions due to metastasis to the hepatic, periaortic, pericaval, retroperitoneal and pelvic areas may play a part in both ascites and leg edema. Hypoproteinemia may also be a factor.

Minor degrees of thickening and scarring of the endocardium of the left side of the heart and of the mitral and aortic valves have been noted, but the scarring and deformity of these valves have not produced significant stenosis or insufficiency. Since many of the patients who were autopsied were over 50 years of age and had vascular sclerosis elsewhere, the minor degrees of sclerosis might have been unrelated to the carcinoid. At present, it is generally believed that the lesions are not entirely localized to the right side of the heart but are definitely more pronounced on the right side. A patent foramen ovale was present at autopsy in two patients and clinically suspected from catheterization findings in one living patient. These may represent instances of the reopening of previously closed foramina by the elevated right atrial pressure resulting from tricuspid incompetency.

The exact cause and nature of the endocardial fibrosis and valvular deformities is not known, but is thought to be related in some manner to the hyperserotoninemia associated with the carcinoid. No stigmata of rheumatic fever or infection has been found in these hearts.

Clinical Features

The clinical features of functioning carcinoid tumors consist of the symptoms and findings related to the mechanical effects of the primary and/or metastatic lesions, and those related to the overproduction of serotonin. For convenience of description they may be divided into the following groups: (1) gastrointestinal, (2) cutaneous vascular, (3) cardiovascular, and (4) metabolic. Features less commonly seen are those associated with the respiratory system, muscle and joints, and the nervous system.

The *gastrointestinal* features are similar to those of the symptomatic, non-functioning carcinoid except that the diarrhea and abdominal pain are more pronounced. The most frequent symptoms and findings are: (1) a long history of intermittent abdominal pain and discomfort, often with recognizable episodes of recurrent partial intestinal obstruction or acute complete obstruction of the small intestine which requires surgery, (2) recurring bouts of diarrhea characterized by frequent watery or semi-liquid stools, often as many as 20 to 30 a day, unassociated with tenesmus or the finding of blood, pus, or mucus in the stools, (3) significant weight loss, (4) hepatomegaly, often with easily felt nodular tumors, and (5) ascites.

The *cutaneous vascular* lesions are the most characteristic and consistently recognized of all the clinical features. These lesions are usually manifested by some form of paroxysmal or persistent erythematous flushing of the skin, predominantly on the face and neck, but variable in extent and location. Various terms have been used to describe the color changes, such as brick red, fiery red, bluish red, mottled bluish red,

purplish red, violaceous, or admixtures of red flushing and patchy cyanosis. Where the cutaneous vascular phenomena have been present for prolonged periods, dilatation of the capillaries and venules of the skin often develops, especially in the face and lower extremities, with the occurrence of miliary and gross telangiectasia. This "peculiar cyanosis" occurs without evidence of arterial oxygen unsaturation.

The spontaneous paroxysm, with rapid changes in appearance and color, is perhaps more striking and diagnostic than the actual color and character of the skin itself. The frequency and the duration of paroxysms, as well as the apparent precipitating factors and associated symptoms, differ greatly in the cases which have been described in detail. The flush may be momentary or it may last for days. It may persist in a mild form on the face with paroxysmal intensification and then spread to other parts of the body. Frequently there is an associated sensation of local heat, tingling, or tightness of the skin and even an appearance of swelling of the skin. Palpitation, tachycardia, dizziness and superficial venoconstriction are common during attacks. Syncope and hypotensive states have occurred. Episodes of flushing occur spontaneously but are described as being provoked by emotional stress, physical exertion, eating, smoking a cigarette, alcohol intake, evacuation of the bowels, or by abdominal, pelvic, or proctoscopic examinations. Episodes have occurred upon palpation of a metastatic carcinoid in the testes[11], palpation of a pelvic mass on pelvic or proctoscopic examination[12], or by massage of hepatic metastases[9]. Histamine, given intravenously, has been considered to initiate episodes of flushing[12]. If these peculiar vasomotor phenomena occur for the first time during or after surgery a functioning carcinoid should be suspected. Distressful tightness in the throat and frank asthmatic symptoms have appeared during the height of flushing. The total duration of recognized cutaneous vascular phenomena before death has been variable. In several instances it was observed to exist over a period of years. In a few patients, it was noted only as a terminal event, but may have been overlooked in earlier examinations.

Cardiovascular Symptoms and Findings

Progressive exertional dyspnea and fatiguability were the most frequent "cardiac" symptoms observed and often were of long duration. Edema of the lower extremities occurred early in some patients and was present in the majority in their terminal months. The clinical features of tricuspid and pulmonary valve lesions were usually recognized prior to death and the lesions were found at autopsy. In some patients, however, the clinical data observed or reported in case reports was too meager to correlate with autopsy findings. In about half of the living patients now under observation who have findings indicative of functioning carcinoids, definite clinical features of right-sided valvular lesions exist. There are several deceased patients who had neither clinical nor autopsy findings of heart lesions but had other clinical features of a functioning carcinoid. It is believed that in the majority of cases the cardiac changes are late manifestations and are not present in patients in whom the condition is recognized early. Several have had catheterization studies of the right side of the heart and angiocardiograms which demonstrate the tricuspid and/or pulmonary valve lesions.

Roentgenographic and electrocardiographic evidence of right ventricular and right atrial hypertrophy is usually seen in patients with clinical evidence of pulmonary or tricuspid valve lesions. Sinus rhythm has been present in all in which an ECG was reported. Right bundle branch block has been reported in two patients. The arterial saturation has been normal except in the few instances where there was a re-opening of a foramen ovale incident to tricuspid insufficiency and high right atrial pressure. Likewise there has been no clubbing of the digits or evidence of polycythemia. These features aid in the differential diagnosis from cyanotic congenital heart disease. The majority of patients had normal blood pressures. A few were described as having marked fluctuations of arterial blood pressures and when carefully evaluated during episodes of cutaneous flushing, hypotension was found. Some of the older patients had elevated blood pressures and hypertensive vascular disease which was probably coincidental.

Clinical asthma, or a peculiar respiratory distress, was noted in 8 of the 38 cases reviewed. It was not a pronounced symptom in any patient, and in reviewing case reports there was difficulty in distinguishing bronchial asthma from cardiac dyspnea. Respiratory stridor and constricting sensations in the chest, particularly with paroxysms of cutaneous flushing, occurred in some patients and may be more significant and diagnostic than bronchial asthma. It is hoped that as more living patients are observed, additional information about these respiratory features may be obtained.

Several patients had frank psychotic episodes and others exhibited peculiar personality changes. These may be merely coincidental. However, since serotonin is now considered an important substance in brain chemistry, and substances chemically related to serotonin are known to produce alterations in cerebral function, these observations may be of significance.

Metabolic and Diagnostic Studies

At the time Thorson and associates[3] suggested that secretion of serotonin might be involved in the pathogenesis of this condition, studies were in progress in the National Heart Institute on the biogenesis and metabolism of serotonin in experimental animals. These studies showed that serotonin was derived from the amino acid, tryptophan, and was metabolized to 5-hydroxyindoleacetic acid (5-HIAA)[8]. Using chemical methods, serotonin was measured in the blood of man, and 5-HIAA was shown to be a constituent of normal urine.

Since September 1954, eight patients with metastatic carcinoid tumors have been studied and urine samples or specimens of tumor tissue were obtained from six additional patients. The blood levels of serotonin in carcinoid patients were shown to range from 0.5 to 2.7 micrograms/cc compared to normal values of 0.1 to 0.3 micrograms/cc. Analyses of several metastatic carcinoid tumors showed both a serotonin content of 0.8 to 3.0 mg./Gm. and the presence of enzymes involved in the formation and destruction of serotonin. The urinary excretion of the serotonin metabolite, 5-HIAA, ranged from 52 to 580 mg. per day in carcinoid patients as compared to 2 to 9 mg. per day in normals. Because of the extreme elevation of urinary 5-HIAA, *its measurement provides a simple and rapid means of recognizing metastatic carcinoid.* A simple qualitative test for 5-HIAA can be done quickly on a few drops of urine[13], but a quantitative assay[14] is required to measure levels of 5-HIAA in amounts less than 30 mg. per day. Up to the present time *the chemical test has afforded a reliable means of diagnosis.*

The precursor relationship of tryptophan to 5-HIAA, and hence to serotonin in man, was shown in these patients. Twenty microcuries of 2-C^{14}-DL tryptophan was administered orally to three patients and urinary 5-HIAA was isolated and found to be radioactive, which indicated its derivation from the administered tryptophan. In metabolic balance studies the daily excretion of 5-HIAA was shown to increase and decrease with corresponding variations in the dietary intake of tryptophan. In carcinoid patients, as much as 60 per cent of dietary tryptophan is converted to urinary 5-hydroxyindoles, whereas, normally only about 1 per cent of ingested tryptophan is metabolized in this manner. Thus, diversion of tryptophan into the serotonin pathway may leave less of the amino acid available for the formation of other metabolites such as niacin and protein. Recent studies which show a reduced fasting blood tryptophan level in some of these patients and diminished urinary excretion of the niacin metabolite, N-methyl-nicotinamide, tend to confirm this hypothesis. The consequences of altered tryptophan metabolism, as well as excess serotonin production, should be considered in concepts of the pathogenesis.

Relation of Chemical Findings to Pathogenesis of Cardiovascular Lesions

The disturbances of smooth muscle function in this disorder, such as hyperperistalsis and bronchoconstriction, are probably direct pharmacologic effects of serotonin. The variability of the cutaneous flushes with associated venoconstriction and hypotension attest to the complicated action of serotonin on vascular smooth muscle. The levels of blood pressure in carcinoid patients are not consistent with the concept that serotonin is a pressor substance in man. Although there is considerable variation in the levels of blood serotonin and urine 5-HIAA from day to day, no success has attended attempts by the authors to relate changes in these values to symptomatology. Furthermore, patients with a comparable degree of metabolic abnormality exhibit widely varying degrees of disability.

The association of acquired valvular disease of the heart with an acquired metabolic defect would appear more than coincidental. Since the experimental counterpart of the cardiac lesion has not been produced, any explanation must be considered tenuous. Our initial impression was that destruction in the lungs of serotonin released by liver metastases might account for the apparent predominance of involvement of the right side of the heart. However, catheterization of four patients has failed to reveal any significant difference in free or bound (to platelets) serotonin levels between mixed venous and peripheral arterial blood. It is our belief that left-sided cardiac involvement may be more common than supposed and that the cardiac lesions are related in some way to the chemical abnormality. The possible importance of hemodynamic alterations associated with flushing episodes is uncertain and in no instance have we encountered an elevation of pulmonary artery pressure such as that which may follow the infusion of serotonin into animals.

Diagnostic Criteria

The presence of secreting carcinoid tumors should be suspected when a variety of circumstances exist. There will be no difficulty in recognizing the full syndrome as described. However, any single sign or symptom may be the sole evidence of the presence of functioning carcinoids. Flushes in one of our patients were initially thought to be of the post-menopausal type. Diarrhea in another patient was considered at various times to be due to bacillary dysentery, amebiasis and functional factors. Another patient was asymptomatic except for two episodes of right upper quadrant pain and was operated upon because of suspected cholecystitis. Functioning carcinoids should be considered in the differential diagnosis of hepatomegaly and valvular heart disease. Finally, this tumor must be considered in patients with metastatic neoplasms which are accompanied by an unexpectedly benign clinical course.

Therapy

Because of the slow growth of both primary and metastatic carcinoid tumors, radical surgical extirpation is indicated even when the tumors cannot be removed completely. In this regard, serial measurements of urinary 5-HIAA will be of unique value in judging the effectiveness of surgery and the course of subsequent tumor growth. Even if they are asymptomatic, localized and mildly invasive, carcinoid tumors should be promptly removed because of their malignant propensities. Since the primary tumor of the malignant carcinoid, as well as the potential functioning carcinoid, occurs most frequently in the lower ileum, it is advisable to inspect and palpate the lower ileum during routine abdominal surgery and if benign lesions are recognized, prophylactic excision is believed justified.

Medical therapy, including irradiation, is generally unsatisfactory. With the possible exception of chlorpromazine, the so-called serotonin antagonists currently available have been ineffective. A high protein diet and vitamin supplements including niacin seem indicated. Other measures are non-specific and constitute the treatment of symptoms and complications. Treatment of heart failure is the same as that for failure from other causes. If pulmonary stenosis or tricuspid stenosis is severe, valvulotomy may be justified. A prompt means of diagnosis, plus knowledge of the chemical alteration induced by the tumor, should lead to more effective therapy of this disorder.

Summary

1. The cardiovascular lesions associated with functioning carcinoid tumors have been described.

2. The association of endocardial and valvular heart lesions with a disorder of tryptophan metabolism opens new concepts in the pathogenesis of heart disease.

3. Prompt recognition and proper surgical therapy of the carcinoid tumor should be stressed in the prevention of this type of heart disease.

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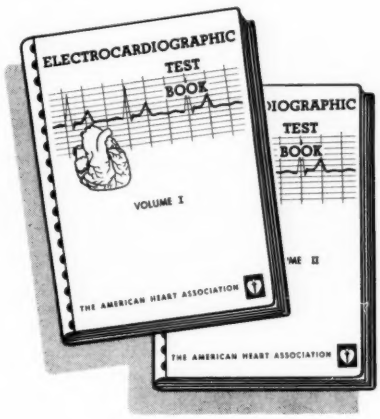

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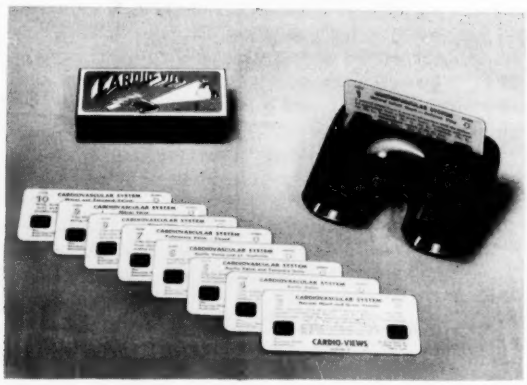

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